

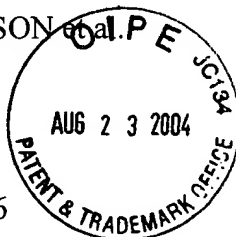
IN THE UNITED STATES PATENT AND TRADEMARK OFFICE  
PATENT EXAMINING OPERATION

Applicant(s): Glen H. ERIKSON et al.

Serial No: 09/885,731

Filed: June 20, 2001

Att. Docket No.: E1047/20056



Group Art Unit: 1637

Examiner: S. Chunduru

Confirmation No.: 6800

For: NUCLEIC ACID MULTIPLEX FORMATION

**APPEAL BRIEF UNDER 37 CFR § 1.192**

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Sir:

I. Introduction

Further to the Notice of Appeal filed May 18, 2004 in response to the April 30, 2004 Final Rejection in which claims 1-5, 7-27 and 29 were finally rejected under 35 U.S.C. § 103(a), Applicants respectfully request reversal of the Final Rejection and allowance of the claims.

A. Real Party in Interest

The real party in interest for this appeal and the present application is the assignee, Ingeneus Corp.

B. Related Appeals and Interferences

Appeals pending in the following application would directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal: U.S. Patent Application Serial No. 09/713,177, filed November 15, 2000. There are presently no other pending appeals or interferences, known to appellant, appellant's representatives or the assignee, that would directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

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C. Status of Claims

Claims 1-5 and 7-55 are pending, with claims 28 and 30-55 being withdrawn from consideration pursuant to a restriction requirement. Elected claims 1-5, 7-27 and 29 are the subject of this appeal and are set forth in the Appendix.

D. Status of Amendments

No amendments have been filed after the appealed Final Rejection dated April 30, 2004.

II. Summary of Invention

The claimed invention relates to methods for forming nucleic acid triplexes and quadruplexes. See claim 1 and the specification at page 1, lines 15-17. Prior to the present invention, the conventional wisdom regarding triplex and quadruplex nucleic acids was that such peculiar structures only exist under relatively extreme conditions for a relatively narrow class of nucleic acids. See the specification at page 3, lines 29-33. The claimed invention provides a method of creating a nucleic acid multiplex (i.e., triplex or quadruplex) with a wide variety of nucleic acids and analogs thereof, wherein the method is conducted in the presence of an accelerator agent (claim 1). Each strand of the multiplex is associated with all other strands of the multiplex by adherence to Watson-Crick base-pairing rules or homologous binding base-pairing rules (claim 1).

Watson-Crick base-pairing rules dictate that A is paired with T, A is paired with U, and G is paired with C (specification at page 11, lines 1-9). A Watson-Crick triplex of the invention comprises base triplets selected from the group consisting of A-T-A, T-A-T, U-A-T, T-A-U, A-U-A, U-A-U, G-C-G and C-G-C (specification at page 8, last paragraph). A Watson-Crick

quadruplex of the invention comprises: (a) a first strand containing a first sequence of nucleobases; (b) a second strand containing a second sequence of nucleobases, wherein said second strand is associated with said first strand by Watson-Crick bonding; (c) a third strand containing a third sequence of nucleobases; and (d) a fourth strand containing a fourth sequence of nucleobases, wherein said fourth strand is associated with said second strand and said third strand by Watson-Crick bonding. See the specification at page 9, lines 1-13.

Homologous binding base-pairing rules dictate that A is paired with A, T is paired with T, G is paired with G, C is paired with C, and U is paired with U (specification at page 12, lines 8-13).

Unlike prior art triplexes and quadruplexes that exist for a relatively narrow class of polypurine or polypyrimidine sequences, the multiplexes produced by the claimed method are based on heteropolymeric strands with a G-C content between 10% and 90% (claim 1), wherein a combined frequency of purine-pyrimidine dimers and pyrimidine-purine dimers in the multiplex exceeds 25%.

### III. Issues

Whether claims 1-5, 7-27 and 29 are not obvious under 35 U.S.C. § 103(a) over U.S. Patent No. 5,451,502 (George) in view of J. Mol. Graphics, Vol. 7, pages 218-232, 1989 (McGavin).

### IV. Grouping of Claims

Each claim of this patent application is separately patentable, and upon issuance of a patent is to be entitled to a separate presumption of validity under 35 U.S.C. §282. However,

pursuant to 37 C.F.R. §1.192(c)(5), for purposes of this appeal, the rejected claims are grouped together in a single group.

V. Argument

Claims 1-5, 7-27 and 29 are not obvious under 35 U.S.C. § 103(a) over U.S. Patent No. 5,541,502 (George) in view of J. Mol. Graph., Vol. 7, pp. 218-232, 1989 (McGavin).

A. No Reasonable Motivation to Modify George with McGavin

George discloses hybridization of single-stranded probes to single-stranded targets. See George at column 6, lines 1-4 (“The first oligonucleotide used in the present invention is a single-stranded oligonucleotide and has a structure complementary to the nucleic acid sequence being detected.”) and at column 9, lines 54-55 (“The assay is initiated by denaturing the sample target molecule to form a single-stranded molecule.”).

McGavin was cited by the Examiner in an effort to remedy George’s acknowledged failure to “specifically teach that . . . each strand of said multiplex structure (probe-target complex) is related to all other strands of the multiplex by Watson-Crick base-pairing rules.” See Final Rejection at page 3, last paragraph. More succinctly, McGavin was cited in an effort to remedy George’s failure to teach triplexes and quadruplexes.

As suggested by the title of McGavin, “A computer graphics study of multistranded DNA models,” McGavin discloses theoretical, computer-based models for multiplex nucleic acid sequences, but does not disclose or suggest how the virtual structures depicted by the computer models could be prepared using real nucleic acids. The application of McGavin to reject the claims is based on an improper “obvious-to-try” standard of obviousness. One skilled in the art

at the time of the invention would have lacked motivation to employ the purely theoretical teachings of McGavin to modify the primary reference, George, and reach the claimed invention with a reasonable expectation of success. McGavin's virtual teachings provide no guidance regarding how George could be modified to reach the reality of the claimed invention. McGavin reveals nothing regarding hybridization conditions, such as temperature, time, hybridization medium, hybridization promoters, etc. McGavin simply "does not contain a sufficient teaching of how to obtain the desired result." See *Gillette Co. v. S.C. Johnson & Son, Inc.*, 919 F.2d 720, 726, 16 USPQ2d 1923, 1929 (Fed. Cir. 1990), in which the court held:

[A]n "obvious-to-try" situation exists when a general disclosure may pique the scientist's curiosity, such that further investigation might be done as a result of the disclosure, but the disclosure itself does not contain a sufficient teaching of how to obtain the desired result, or that the claimed result would be obtained if certain directions were pursued. *In re Eli Lilly & Co.*, 902 F.2d 943, 945, 14 USPQ2d 1741, 1743 (Fed. Cir. 1990). However, we have consistently held that "obvious to try" is not to be equated with obviousness under 35 U.S.C. §103.

The Examiner alleges that "[a]n ordinary artisan would have [been] motivated to have added the structural stability of Watson-Crick base pairing of nucleic acid strands in a multiplex structure to the method of George, Jr., because McGavin et al. taught Watson-Crick kind of base pairing as a strong specific interaction between complementary strands and its growing significance in genetic combination or specificity of interaction between stands." See Final Rejection at the paragraph bridging pages 4-5. The Examiner has not identified precisely where McGavin supports this assertion. Presumably, the assertion is based on the following two passages from McGavin:

(1) “Watson-Crick base pairing is clearly a more strongly specific interaction than the additional interaction that we have used to form base tetrads from Watson-Crick base pairs.” McGavin at page 230.

(2) “One such model. . . has proved to be of considerable interest, perhaps particularly in relation to models for genetic recombination.” McGavin at page 225.

It should be apparent from the two passages that the motivation alleged by the Examiner is taken out of context. The first passage discloses that the quadruplex (i.e., “tetrad”) binding interactions postulated by McGavin are inferior to conventional Watson-Crick duplex binding, and the second passage merely suggests that McGavin’s new model might be used as a model to study genetic recombination (presumably mitosis and the like, wherein more than two strands interact on some basis).

The foregoing disclosures of McGavin would not have motivated a person of ordinary skill in the art to modify the teachings of George to reach the claimed invention. Regardless of whether McGavin would have motivated an ordinarily skilled artisan to select a Watson-Crick quadruplex over another type of quadruplex, the Examiner has made absolutely no showing as to why such an artisan would have been motivated to replace the conventional Watson-Crick duplex probe-target complexes of George with the speculative Watson-Crick quadruplexes (or triplexes) of McGavin, which McGavin teaches are based on binding that is not as “strongly specific” as Watson-Crick pairing of two strands. There is no reasonable basis to contend that one skilled in the art would have understood from McGavin that Watson-Crick multiplexes were more specific and of greater scientific potential than conventional Watson-Crick duplexes.

Moreover, the speculative nature of McGavin, as well as the complete lack of any teaching regarding how to prepare real counterparts of the computer models, would have discouraged a person of ordinary skill in the art from attempting to substitute McGavin's triplexes or quadruplexes for George's duplexes, such that he or she would have had no reasonable expectation of success. A reference, such as McGavin, containing a statement such as "[w]e have indeed come to think of the use of this core as a model building 'game,'" would not have motivated an ordinarily skilled artisan to modify with a reasonable expectation of success an experimentally proven technology employing a Nobel prize winning duplex model.

Accordingly, the claimed invention is not *prima facie* obvious over George in view of McGavin, as the Examiner has not shown that one of ordinary skill in the art would have been motivated to modify the teachings of George with the teachings of McGavin, and reach the claimed invention with a reasonable expectation of success. See, e.g., MPEP § 2143.

B. McGavin is Improperly Cited Non-enabling Art

A reference relied upon to support an obviousness rejection must provide an enabling disclosure by placing the claimed invention in the possession of the public. See, e.g., *In re Payne*, 606 F.2d 303, 203 USPQ 245, 255 (CCPA 1979). "[I]f the prior art of record fails to disclose or render obvious a method for making a claimed compound, at the time the invention was made, it may not be legally concluded that the compound itself is in the possession of the public." *In re Hoeksema*, 399 F.2d 269, 274 (CCPA 1968).

In *Hoeksema*, the court held that the examiner had made a *prima facie* case of obviousness by citing a reference disclosing a compound analogous to the claimed compound

and a method for making the analogous compound. Applicants in *Hoeksema* submitted an affidavit showing that the claimed compound could not be made by the process disclosed in the applied reference. The court held that the affidavit overcame the *prima facie* showing by showing that the applied reference was not enabling.

In contrast to the applied reference of *Hoeksema*, McGavin does not disclose any process for preparing any chemical compound. As noted above, McGavin discloses theoretical, computer-based models for multiplex nucleic acid sequences based on Watson-Crick bonding, but does not disclose or suggest how to prepare real complexes of nucleic acids corresponding to the virtual models.

Moreover, identifying the chemical formula of a compound that fits within conventional rules of chemistry, as in *Hoeksema*, is far different from building virtual models of multiplex nucleic acids that contravene conventional rules of nucleic acid assembly at the time of the invention, as in McGavin. It is unreasonable to presume that a method for preparing the latter exists from a wholly theoretical reference.

In the Final Rejection at pages 5-6, the Examiner cites MPEP § 2121.04 as supporting an obviousness rejection based on pictures. However, even the cited passage of the MPEP cautions that “the picture must show all the claimed structural features *and how they are put together.*” [Emphasis added.] While Applicants agree that pictures of a simple mechanical apparatus can inherently reveal how to assemble the apparatus, computer generated pictures depicting a virtual model of nucleic acid strands associated in an unprecedented fashion do not reveal anything about how to prompt nucleic acid strands to assemble in such a fashion. McGavin speculates as



to how the nucleobases of multiplex structures might fit together, like pieces of a jigsaw puzzle. Unlike a jigsaw puzzle, however, real world assembly of the multiplex “puzzle” is not simply a matter of snapping adjacent pieces of the puzzle into place.

Thus, the PTO has not sustained its initial burden of making a *prima facie* showing that the claimed methods for making multiplexes of the invention were known or obvious in the art at the time of the invention.

C. Consistency of Positions

The Examiner asserts that Applicants’ arguments are inconsistent with their previous citation of McGavin in response to the previously pending non-enablement rejection of the claims. Applicants respectfully disagree. A brief review of the prosecution history related to this issue will be helpful in understanding why there is no inconsistency in Applicants present and past positions.

Applicants in their July 21, 2003 Amendment cited McGavin (and several other related McGavin references) as only one of several factors suggesting the reasonable credibility of the invention. Applicants never said that McGavin provides even the slightest suggestion regarding how to make a real chemical compound corresponding to the computer models disclosed therein. McGavin was simply cited to provide space filling model evidence supporting the *reasonable credibility* of W-C base bonding involving more than two strands, as requested by the Examiners in the parent application. See July 21, 2003 Amendment at the paragraph bridging pages 10-11. See also July 21, 2003 Amendment at page 13, second full paragraph, stating that McGavin’s “quantitative calculations suggesting the thermodynamic favorability of four-stranded Watson-

Crick complexes lend further credence to the existence of such complexes and the invention claimed by Applicants.”

McGavin was only one aspect of Applicants’ response to the non-enablement and lack of utility rejections. See July 21, 2003 Amendment at page 13, third full paragraph. The present invention is enabled by the specification, which includes working examples suggesting the formation of the claimed multiplexes, and McGavin provides additional evidence supporting the reasonable credibility of such multiplexes.

In summary, the Examiner has asserted that the multiplex structures of the invention were theoretically impossible, and Applicants cited McGavin as evidence that multiplex structures were theoretically possible. Referring back to the jigsaw puzzle analogy first mentioned above, the Examiner doubted whether the puzzle pieces could fit together. McGavin was cited as evidence that the puzzle pieces could be arranged in a manner consistent with the claimed invention, without ever asserting that assembly of the multiplex “puzzle” is simply a matter of snapping adjacent pieces of the puzzle into place. Applicants disclose and claim means for assembling the real world counterpart to the virtual puzzle.

Accordingly, the claimed invention is not obvious under 35 U.S.C. § 103(a) over George in view of McGavin.

#### VI. Conclusion

The claims on appeal are not obvious under 35 U.S.C. §103(a) over George in view of McGavin. Accordingly, the Honorable Board of Patent Appeals and Interferences is respectfully requested to withdraw the pending rejection and pass this application on to issuance.

Application No. 09/885,731  
Appeal Brief Dated August 18, 2004  
Reply to Final Rejection of April 30, 2004

The fee of \$165.00 for this Brief, as well as any additional charge or credit, is authorized to be charged to the Deposit Account referenced in the accompanying Form PTO/SB/17. Triplicate copies of this Brief are provided.

Respectfully submitted,

CAESAR, RIVISE, BERNSTEIN,  
COHEN & POKOTILOW, LTD.

August 18, 2004

Please charge or credit our  
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By



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**Appendix: Claims on Appeal**

1. A method of creating a nucleic acid multiplex, said method comprising the steps of:

1) creating a mixture comprising water, a Watson-Crick duplex, a sufficient number of single-stranded mixed base sequence molecules to form the multiplex including the Watson Crick duplex, and an accelerator agent that increases a rate or amount of multiplex formation, said multiplex being a triplex or quadruplex; and

2) incubating said mixture to allow the multiplex to form, each strand of said multiplex related to all other strands of the multiplex by adherence to Watson-Crick base-pairing rules or homologous binding base-pairing rules;

provided that, within the multiplex, the Watson-Crick duplex added in step (1) is heteropolymeric with a G-C content between 10% and 90% and a combined frequency therein of purine-pyrimidine dimers and pyrimidine-purine dimers exceeds 25%.

2. A method of Claim 1 wherein the multiplex created is a triplex, in step (1) the sufficient number of single-stranded molecules is 1, and in step (2) the triplex is formed.

3. A method of Claim 1 wherein the duplex substantially retains its double-helical structure and the single-stranded molecule resides in a groove of that double-helical structure.

4. A method of Claim 1 wherein the single-stranded molecule is related to one strand of the duplex by Watson-Crick base-pairing rules and to the second strand of the duplex by homologous binding base-pairing rules.

5. A method of Claim 4 wherein the duplex substantially retains its double-helical structure and the single-stranded molecule resides in a groove of that double-helical structure.

7. A method of Claim 1 wherein steps (1) and (2) are performed with at least one of the nucleic acid strands and the duplexes not in a cell.

8. A method of Claim 1 wherein step (2) is performed without assistance of a protein.

9. A method of Claim 1 wherein in step (1), the water is added so that it accounts, on a volume basis, for at least 50 percent of a final volume of the mixture.

10. A method of Claim 1 wherein in step (1), the water is added so that it accounts, on a volume basis, for at least 80 percent of a final volume of the mixture.

11. A method of Claim 1 wherein in step (1), the water is added so that it accounts, on a volume basis, for all of the liquid added to the mixture.

12. A method of Claim 1 wherein step (2) is performed at a temperature or temperatures above a freezing temperature of the mixture and at not more than 85°C.

13. A method of Claim 12 wherein the temperature or temperatures is/are 5 °C to 30 °C.

14. A method of Claim 13 wherein the temperature or temperatures is/are 15 °C to 25 °C.

15. A method of Claim 1 wherein in step (1), a cation is added as the accelerator agent.

16. A method of Claim 15 wherein said cation is Na<sup>+</sup> provided at a concentration of 50mM to 125mM.

17. A method of Claim 15 wherein said cation is selected from the group consisting of Mn<sup>+2</sup> provided at a concentration of 10mM to 45mM, Mg<sup>+2</sup> provided at a concentration of 10mM to 45mM, and Ni<sup>+2</sup> provided at a concentration of 20mM.

18. A method of Claim 1 wherein in step (1) an intercalator is added as an accelerator agent.

19. A method of Claim 18 wherein the intercalator is a fluorescent intercalator.

20. A method of Claim 19 wherein the fluorescent intercalator is selected from the group consisting of YOYO-1, TOTO-1, YOYO-3, TOTO-3, POPO-1, BOBO-1, POPO-3, BOBO-3, LOLO-1, JOJO-1, cyanine dimers, YO-PRO-1, TO-PRO-1, YO-PRO-3, TO-PRO-3, TO-PRO-5, PO-PRO-1, BO-PRO-1, PO-PRO-3, BO-PRO-3, LO-PRO-1, JO-PRO-1, cyanine monomers, ethidium bromide, ethidium homodimer-1, ethidium homodimer-2, ethidium derivatives, acridine, acridine orange, acridine derivatives, ethidium-acridine heterodimer, ethidium monoazide, propidium iodide, SYTO dyes, SYBR Green 1, SYBR dyes, Pico Green, SYTOX dyes, and 7-aminoactinomycin D.

21. The method of Claim 1 wherein the accelerator agent is a non-intercalating fluorophore.

22. A method of Claim 21 wherein the non-intercalating fluorophore is selected from the group consisting of biotin, rhodamine, Alexa dyes, BODIPY dyes, biotin conjugates, thiol-reactive probes, fluorescein and derivatives including but not limited to the caged probes, Oregon Green, Rhodamine Green, QSY dyes.

23. A method of Claim 1 wherein in step (1) the accelerator agent is an intercalator that binds to at least one of the minor groove and the major groove of the Watson-Crick duplex.

24. The method of Claim 1 wherein in step (1) the accelerator agent at 25 °C is a liquid.

25. The method of Claim 24 wherein in step (1) the accelerator agent is an organic liquid soluble in water.

26. The method of Claim 1 wherein in step (1) an accelerator agent that is a condensation agent as regards the Watson-Crick duplex is added.

27. The method of Claim 1 wherein in step (1) an accelerator agent that is a decondensation agent as regards the Watson-Crick duplex is added.

29. A method of Claim 1 wherein the multiplex created is a quadruplex, in step (1) the Watson-Crick duplex is a first Watson-Crick duplex, and in step (1) the sufficient number of single-stranded molecules is 2, those single-stranded molecules are in a second Watson-Crick duplex, and in step (2) the quadruplex is formed from said first and second duplexes.